The prevalence and in-hospital mortality of patients with HIV and tuberculosis admitted to the resuscitation area of an urban district-level hospital in Cape Town

by

Lynne Swarts

Division of Emergency Medicine

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Supervisor: Dr. Daniël Jacobus van Hoving

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Declaration

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Table of Contents

Part A: LITERATURE REVIEW

Introduction

The global burden of HIV and tuberculosis

Human Immunodeficiency Virus (HIV) has been recognised as one of the most devastating epidemics in recent history, since it was first recognised in the 1980's [1]. The number of people living with HIV (PLHIV) in 2016 was estimated at 36.7 million, with 1.8 million new infections and 1 million Acquired Immune Deficiency Syndrome (AIDS) related deaths recorded [2]. Resource-limited countries are more affected, with the majority of PLHIV from Sub-Saharan Africa (64%) [2]. In recent years, the overall global trend related to an increased HIV prevalence alongside a substantial decline in AIDS-related deaths [3]. These trends are largely attributable to the increased use and availability of anti-retroviral medications [3].

Tuberculosis is as devastating and has been proven to be one of the top 10 causes of death worldwide [4]. In 2017 alone, an estimated 10 million people developed tuberculosis, whereas 1.6 million people died from tuberculosis (1.3 million HIV-negative and 300 000 HIV-positive) [4]. Currently, 23% of the world's population (about 1.7 billion people) are estimated to have latent tuberculosis infection and are therefore at risk of developing active tuberculosis disease during their lifetime [4]. Increased awareness and access to antituberculosis medication has resulted in a steady decline in the global absolute number of tuberculosis deaths in both HIV-negative and HIV-positive people [4].

HIV and tuberculosis co-infection is often seen as a lethal combination, causing numerous diagnostic and therapeutic challenges in affected individuals [5]. A complex but well described relationship exists between HIV and tuberculosis - the more advanced the degree of immunodeficiency, the higher the risk of contracting tuberculosis [6,7]. Tuberculosis still remains one of the leading causes of HIV-associated morbidity and mortality worldwide, affecting both adults and children [8]. In 2017, 300 000 of 940 000 (32%) HIV deaths, globally, occurred among people co-infected with HIV and tuberculosis; this has shown a decline in recent years [9]. However, many cases of tuberculosis in PLHIV are only diagnosed post-mortem at autopsy, which suggest that tuberculosis-related HIV deaths may be even more prevalent [10]. On a global scale, an equivalent of 12% of patients with notified tuberculosis disease had a documented HIV positive result in 2017, of which the highest burden (72%) was accounted for by the World Health Organization (WHO) African region [4]. Despite increased access to anti-retroviral treatment (ART) and improved life expectancy in recent years, HIV prevention strategies and education remain insufficient, with no known cure as yet [11].

The South African HIV and tuberculosis burden and relevance

Sub-Saharan Africa accounts for about 71% of the global HIV burden, yet only houses about 12% of the world's total population [3].

The incidence and mortality of tuberculosis in South Africa appear to be declining, as a result of increased awareness and the use of anti-tuberculosis medications. This decline is regrettably not fast enough to meet the 2030 Sustainable Development Goals or the 2035 End TB Strategy targets [12]. In order to meet these targets, the WHO estimates that by 2030, tuberculosis incidence rates for South Africa would need to decrease to 167 per 100 000 population and decrease to 83 per 100 000population by 2035 [12]. There were an estimated 454 000 incident tuberculosis cases in South Africa in 2015, at a rate of 834 cases per 100 000 population, with the highest global burden of HIV co-infection [1]. South Africa is also on the WHO's list of the top 20 highest estimated number on incident tuberculosis cases in the world [4] and is one of six countries accounting for 60% of the global tuberculosis burden [12].

Late presentation and non-diagnosis of tuberculosis and HIV

Many patients in South Africa still do not know their tuberculosis or HIV status, despite extensive rollouts of tuberculosis and HIV prevention plans and allocated financial resources [13,14]. Multiple factors attribute to this, including stigmatisation, long waiting times at healthcare facilities, denial, and fear of discrimination [15,16]. These patients are often only diagnosed late in their disease course, some patients not even at all, and do not obtain the full benefit from available treatment and HIV/tuberculosis care services [16]. The presence of HIV infection often complicates the clinical presentation of active tuberculosis, particularly in patients with advanced immunocompromised states [17]. Such patients may present with little to no symptoms of active tuberculosis, non-specific symptoms only (fatigue, weakness, anaemia) and decreased specificity of diagnostic testing (normal appearance on chest x-rays, smear-negative sputum results), thus leading to diagnostic inaccuracy and delayed diagnosis [17]. It is well established that delay in diagnosis and treatment of these conditions result in increased morbidity, economic loss to the patient, increasing numbers of emergency presentations and an increased mortality [12,18-20].

HIV and tuberculosis-related emergencies

Disease burden and morbidity is mainly dictated by disease prevalence. South Africa is currently facing the crisis of a quadruple burden of disease, which seem to be more prevalent

in the socio-economically deprived regions, where resources are limited and education is lacking [21]. In resource limited settings with a high HIV prevalence, medical emergencies related to tuberculosis and HIV frequently presents to emergency care facilities, especially in more advanced disease states [22]. Such individuals are thus more susceptible to severe (often opportunistic) infections involving multiple organ systems, including involvement of the respiratory tract, cardiovascular-, gastrointestinal- and central nervous systems. Frequent HIV and/or tuberculosis-related presentations to emergency centres include systemic septicaemia, pneumonia, meningitis, thrombo-embolic phenomena (deep vein thrombosis and pulmonary embolism), massive haemoptysis, acute respiratory distress syndrome (ARDS), acute and chronic gastroenteritis, encephalopathy and pericardial disease [22-25]. Unique patterns of disease are also encountered in HIV-positive individuals, such as HIV-related chronic kidney disease (HIVAN), cardiomyopathies and neuro-cognitive disorders [26–28]. Clinicians require high level of suspicion, time to investigate patients adequately and knowledge of these potential complications to make accurate diagnoses in high-risk patients.

Anti-retroviral therapy and anti-tuberculosis treatments are also associated with numerous and potentially life-threatening side effects. Immune-reconstitution inflammatory syndrome (IRIS), cutaneous adverse drug reactions (e.g. Steven Johnson syndrome and toxic epidermal necrolysis), and drug induced liver injury (DILI) have been well described in the literature and are frequently encountered in high prevalence settings [29–31].

Diagnosis and management of HIV and tuberculosis related emergencies require knowledge of the diseases' pathophysiology, an appropriate rapid assessment and early initiation of treatment. Adequate resources should also be available to ensure effective and efficient care [23].

The South African healthcare system and the distribution of resources

South Africa's healthcare system is often said to be fragmented and unequal, with numerous challenges and few solutions [32]. It consists of a large public sector (serving approximately 82% of the country's population), a smaller private sector that is largely funded by subscriptions of patients to medical aid schemes or private paying patients, and non-government organisations (NGOs) [33]. Wealthier citizens are thought to enjoy the benefits of world class healthcare with the luxury of timeous consultations, better facilities and improved infection control measures [34]. The South African district health system has 52 districts among its 9 provinces [12], with 4200 public primary health-care facilities which provide health care equivalent to 1 facility per 13 718 people, exceeding current WHO guidelines of 1 facility to 10 000 people [33]. This reflects

the major burden of healthcare and disease that is placed on the public health system, along with issues of limited resources, shortage of healthcare professionals and poor infrastructure [33].

Emergency centres/emergency care capacity

At the heart of every hospital is the emergency centre and forms the direct point of entry to patients in need of emergency care [35]. The emergency centre is defined as a dedicated area within a health facility, providing services 24 hours a day, equipped with facilities and resources to provide a high standard of emergency care to community members who require acute or urgent care [35]. The emergency centre is typically the busiest and most unpredictable of all hospital departments, seeing a vast range of presenting complaints from patients of all ages and degrees of health. The urgency with which patients are to be seen and assessed is determined by the South African Triage Scale (SATS) [36], which categorises patients into colour coded groups according to their presenting complaints and vital signs. Each colour code has suggested waiting times for patients to be seen and assessed. The triage colour codes and waiting times are as follows: [36]

- Red (emergency) to be seen immediately
- Orange (very urgent) to be seen in under 10 minutes
- Yellow (urgent) to be seen in under 1 hour
- Green (non-urgent) to be seen in under 4 hours
- Blue (deceased) to be certified by doctor in under 2 hours

It is not always possible for facilities to keep to these recommended time frames, depending on patient load and health care provider availability [37]. This suggests that emergency centre capacity for urgent care is often outweighed by limited human and physical resources. Another additional problem that the emergency centre often faces is patients presenting with complaints that can be dealt with at primary health care (PHC) level, usually with a green triage score [38–41]. Multiple factors can attribute to this, including long waiting times at PHC facilities, patient perception that care is better at bigger hospitals and lack of after hour services [42].

Every emergency centre is required to have a resuscitation area, usually reserved for patients requiring immediate assessment and often life-saving interventions [35]. Although no strict universal criteria exist for patients to be admitted to or managed in a resuscitation area, it is generally accepted that the most critically ill and injured patients receive treatment there,

determined by either a high SATS acuity score or at the discretion of a senior clinician [36], taking into account individual facility's resources and protocols.

The HIV and tuberculosis burden on the emergency centre

Limited data is available on disease burden specific to the resuscitation area, however one study has described a case mix of patients managed in a district level resuscitation area, including trauma and medical emergencies. HIV featured as the most commonly presenting comorbidity (23%), but this figure may not be a true reflection of the actual HIV burden, as HIV is not routinely tested for or documented in trauma-related cases [43].

A 2014 study in Botswana analysed presentations to a tertiary level emergency centre where the majority of presenting complaints were infection related. This study, however, did not elaborate on the kind of infections treated; even though the country has a high HIV prevalence, neither tuberculosis nor HIV specific infection was described, and the authors often grouped multiple infective pathologies into one category [44]. The study also did not specify in which area of the emergency centre these patients were seen or treated.

The feasibility of point-of-care HIV testing in the emergency centre has been shown in a Ghanaian study in 2014, where the prevalence and proportion of emergencies co-morbid with HIV were not accurately characterised. Patients presenting to the emergency centre for various reasons were offered rapid HIV testing; 41% of patients declined. The prevalence of HIV as a comorbidity was described in 13.5% of patients who had consented to HIV testing, compared to the national prevalence of 1.4% at the time [45]. This may reflect differences in health seeking behaviour or lack of HIV testing amongst the general population. The study assessed the association of certain variables (education level, religion, occupation, marital status) and presentations with HIV, but did not analyse tuberculosis status or the burden of HIV on specific areas of the emergency centre.

The need to obtain a deeper insight into the HIV/tuberculosis burden on district level hospitals in South Africa, particularly in regions with high disease prevalence, is especially important to improve health care education and allocate resources in the country. There is very little published research on the ability of South African emergency centres to deal with this pandemic, however, a study conducted at a district level emergency centre in KwaZulu-Natal (where the HIV prevalence is the highest in the country) has shown some considerable insight. The prevalence of HIV in the sample of patients who presented to the emergency centre was

noted to be considerably higher than the South African national prevalence (50% vs 17.9% in 2012), with approximately 37% of patients not having a confirmed or known HIV diagnosis. Respiratory pathology was the leading cause of presentation to the emergency centre, and tuberculosis on top of the list of causes of mortality [46]. Even though the study did not focus on the resuscitation area of the emergency centre, and findings not generalisable to the rest of the South African district health care services, it serves as a good starting point for further and more specific research into the burden of HIV and tuberculosis on emergency care services.

Conclusion

There is a general paucity of data available for cases managed in resuscitation areas in South Africa, particularly relating to the HIV and tuberculosis burden. Even though South Africa has taken major strides to tackle this double-edged sword, the true disease burden and impact on district level settings still needs to be determined in order to ascertain the level of resources (human and material) required to treat these patients. Late and misdiagnosis of HIV and tuberculosis may be prevented with point-of care testing if offered to patients presenting for treatment to emergency centres, possibly leading to earlier initiation of treatment and reduction in emergency complications and presentations of these disease entities. A higher level of clinical suspicion and time for investigation is required with high risk patients, which is not often afforded in the busy and overpopulated emergency centre setting. As HIV and tuberculosis are not issues that are likely to be resolved in our lifetime, it is important to gain more knowledge and insight into this arena to improve quality of care, adequate supply and utilisation of resources at district level hospitals.

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Part B: MANUSCRIPT IN ARTICLE FORMAT

Title page

The prevalence and in-hospital mortality of patients with HIV and tuberculosis admitted to the resuscitation area of an urban district-level hospital in Cape Town

Lynne Swarts[a,*]; Sa'ad Lahri[b]; Daniël Jacobus van Hoving[a]

[a]Division of Emergency Medicine, Stellenbosch University, Cape Town, South Africa

[b]Khayelitsha Hospital, Cape Town, South Africa

*Corresponding author: PO Box 241, Cape Town, 8000; +27 21 938 9804; drlynneswarts85@gmail.com

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Abstract

Introduction

Many patients present to emergency centres with HIV and tuberculosis related emergencies. Little is known about the influence of HIV and tuberculosis on the resuscitation areas of district-level hospitals. The primary objective was to determine the prevalence and in-hospital mortality of patients with HIV and/or tuberculosis presenting to the resuscitation area of Khayelitsha Hospital, Cape Town.

Methods

A retrospective analysis was performed on a prospectively collected observational database. A randomly selected 12-week sample of data was used. Trauma and paediatric (< 13 years) cases were excluded. Patient demographics, HIV and tuberculosis status, disease presentation, investigations and procedures undertaken, disposition and in-hospital mortality were assessed. HIV and tuberculosis status were determined by laboratory confirmation or from clinical records. Descriptive statistics are presented and comparisons for categorical data were done using the χ^2-test.

Results

A total of 370 patients were included. HIV prevalence was 38.4% (n=142; unknown status n=78, 21.1%) and tuberculosis prevalence 13.5% (n=50; unknown status n=233, 63%). The HIV/tuberculosis coinfection rate was 10.8%. Age (mean 42.5 years) and gender distribution (male 40.3%) were similar amongst HIV and tuberculosis groups. Intentional overdose presentations were more frequent in the HIV positive group (14.8% vs 8.7%, $p<0.01$). HIV-negative patients were less likely to receive an abdominal ultrasound examination ($p<0.01$) to aid in excluding extra-pulmonary tuberculosis and received less intravenous antibiotics ($p<0.01$). In-hospital mortality was 17% and was not influenced by HIV status ($p=0.27$) or tuberculosis status ($p=0.27$).

Conclusion

This study highlights the influence of both HIV and tuberculosis on the resuscitation area of a district level hospital. Neither HIV nor tuberculosis status were associated with in-hospital

mortality. The high prevalence of intentional overdose may reflect underlying social concerns that need to be addressed.

Keywords: Emergency Centre; HIV; Tuberculosis; Prevalence; In-hospital mortality

Introduction

The Human Immunodeficiency Virus (HIV) poses a substantial healthcare burden on a global scale, particularly in socio-economically deprived regions.[1] In 2018, approximately 37.9 million people were living with HIV, with an estimated 1.7 million becoming newly infected and 770 000 dying from AIDS (Acquired Immunodeficiency Syndrome) related illnesses.[2] Sub-Saharan Africa accounts for almost 70% of the global HIV incidence, with South Africa being one of the top 10 countries contributing to the burden.[3] In 2017, South Africa's HIV-prevalence was 12.6% (7 million people),[4] while the Western Cape had an HIV prevalence of 6.6% in 2015/2016 (incidence 19 396 per 100 000 population).[5] HIV was also associated with 6.1% (n=3061) of all deaths in the Western Cape in 2015.[6]

Tuberculosis (pulmonary and extra-pulmonary) adds a similar burden. An estimated 10.4 million people were diagnosed globally with tuberculosis in 2016, with 25% of cases reported from the World Health Organization African region.[1] In the same year, the South African tuberculosis incidence was 520 per 100 000 persons, with a Western Cape incidence of 681 per 100 000 population.[7]

Globally, in 2015, 1.2 million patients with tuberculosis (11%) were also found to be HIV positive.[8] Fifty seven percent of South Africans with tuberculosis had a documented HIV-positive status in 2016,[7] with 39% of all newly diagnosed tuberculosis patients in the Western Cape being HIV-positive.[7]

The prevalence of HIV and tuberculosis related emergencies is dictated by disease prevalence, the availability of treatment and the expertise of the health care system. HIV infection is also associated with non-tuberculosis related complications. Serious and possibly life-threatening complications can relate to the respiratory system (bacterial pneumonia, Pneumocystis jiroveci pneumonia), the cardiac system (pericardial disease, cardiomyopathy) and the neurological system (cryptococcal meningitis, toxoplasmosis),[9] but essentially any organ system can be involved.

Patients with HIV and tuberculosis are able to access HIV and anti-tuberculosis treatment via numerous primary health care institutions across South Africa.[10] However, many of these patients still present to emergency centres, particularly with HIV and tuberculosis related emergencies. There is a perception amongst health care personnel that patients with HIV and tuberculosis place a large burden on the emergency centre.[11] Despite studies conducted within emergency centres in South Africa and the Western Cape, no studies have specifically described the burden of HIV and tuberculosis within emergency centres.[12–14]

The primary objective of this study was to determine the prevalence of HIV and tuberculosis in patients presenting to the resuscitation area of the Khayelitsha Hospital. The secondary objective was to determine the association of HIV and tuberculosis status to in-hospital mortality.

Methods

Study design

A retrospective analysis was performed on a prospectively collected observational database. A supplementary chart review was performed to include additional variables and to limit missing data.

Setting

Khayelitsha Hospital is a 300-bed district-level hospital situated in the constantly expanding informal settlement of Khayelitsha, Cape Town.[15] It services a large, socio-economically challenged health district (population > 500 000 people) with high levels of unemployment (38%), interpersonal violence, and a high disease burden of tuberculosis and HIV.[16] The hospital provides in- and outpatient medical, surgical, paediatric and obstetric services. There is also an emergency centre that manages approximately 35 000 patients per annum with an admission rate of about 30%. The emergency centre is 30% larger than for a standard district level hospital in South Africa,[15,16] with a five-bed (including one paediatric cot) dedicated resuscitation area. The area is equipped with monitoring devices (blood pressure, pulse oximetry, capnography, etc.) and acute capabilities for airway management, ventilation and defibrillation. It is the only area outside of the operating theatre where patients can be continuously monitored, as the hospital has no high care or intensive care facilities. The main

admission criteria to the resuscitation area is based on a high acuity score according to the South African Triage Scale,[17] or at the discretion of the senior medical practitioner on duty.

Study population and sampling strategy

The electronic Khayelitsha Hospital Emergency Centre database is an ongoing, prospectively collected observational database and has previously been described.[13] Data are captured electronically, immediately coded and stored onto a password protected server, with a separately stored decoding sheet.

A randomly selected 12-week sample (obtained between 1 November 2014 and 16 August 2015) was obtained from the database, using a computer-based random number generator. The 12-week sample of data was deemed sufficient to fulfil the requirements of the pre-determined objectives of the study, while also considering time and resource constraints. All patients admitted to the resuscitation area during this time period were eligible for inclusion, with exception of paediatric (< 13 years) and trauma related cases.

Data collection

Data have been collected by the investigators on site after a decoded, cleaned extract of the electronic database was obtained (cleaned: copied onto an Excel spreadsheet with all trauma and paediatric cases removed). The password protected Microsoft Excel® spreadsheet was then further populated by reviewing patients' electronic clinical records. Laboratory results not documented in the patient records were added by accessing the National Health Laboratory Service (NHLS) web view. NHLS data were double checked using patient name and date of birth to include results from all public health facilities that the patient may have attended.

Variables collected include patient demographics (age, gender), tuberculosis status (and treatment status if indicated), and HIV status (including CD4 lymphocyte count and antiretroviral use if HIV-positive). Patient acuity was measured using the South African Triage Scale, which categorises patients as Emergency (Red), Very urgent (Orange), Urgent (Yellow), and Non-urgent (Green).[17] Data relating to patient's stay in the resuscitation area included admission category, diagnostic tests performed, interventions received, disposition from and time spent in the resuscitation area. Admissions were categorised based on physiologic systems involved (e.g. cardiovascular, gastro-intestinal, respiratory etc.) as opposed to the final clinical diagnosis or disease process. The all-cause in-hospital mortality of patients was also collected.

An HIV-positive case was defined as a laboratory confirmed result (either prior to admission or during the admission). Patients with an unknown HIV status were reported and analysed as such. An active tuberculosis case was defined as laboratory confirmed result from any clinical specimen during the current admission, six months prior to admission, six months after admission, or patients who have been empirically diagnosed with active tuberculosis and started on anti-tuberculosis treatment. These results have been verified on the NHLS web view using the patient's folder number, initial and surname, or date of birth as filter criteria. Patients' clinical response to anti-tuberculosis treatment was not assessed. This is usually done at the primary health care level, and the emergency centre does not have access to these records. Patients were only tested for tuberculosis and /or HIV on clinical suspicion of the treating physician if the result was to affect the clinical management or outcome of the presenting complaint and not as a routine investigation. Additional investigations for tuberculosis included abdominal ultrasound (either as point-of-care by treating doctors or formal scans performed by radiographers).

Data analysis

Analysis was done using Microsoft Excel® and SPSS Statistics for Windows, Version 25.0 (IBM Corp. Released 2017. Armonk, NY: IBM Corp.). Patients with incomplete information have been excluded from analysis for those variables where information was missing. Summary statistics have been used to describe all variables. Distributions of variables are presented with frequency tables. The prevalence of HIV, tuberculosis and HIV/tuberculosis co-infection was calculated using the total number of patients in the sample as the denominator. The denominator for HIV and tuberculosis categories only included patients of whom the status could be determined as described above (i.e. unknown status was excluded). Data were categorized into four nominal variables to enable the comparison of in-hospital mortality: i) No active tuberculosis and HIV-negative, ii) No active tuberculosis and HIV-positive; iii) Active tuberculosis and HIV-negative, and iv) Active tuberculosis and HIV-positive. Pearson's χ^2-test or Fisher's exact test were used for comparing proportions, and the independent samples t-test to compare medians. A 5% significance level was applied.

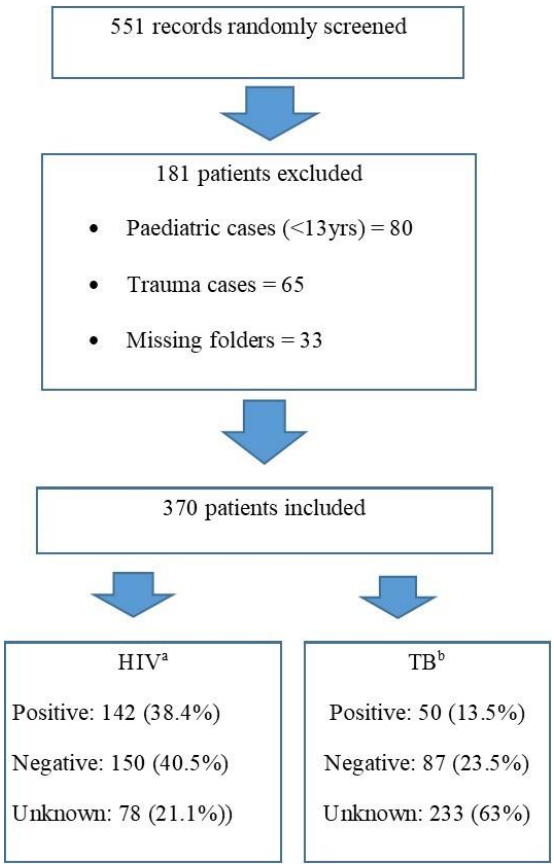
Ethical considerations

The study has been approved by the Stellenbosch University Health Research Ethics Committee (Ref: S15/10/243). The database from which the initial data was drawn is registered with the Stellenbosch University Health Research Ethics Committee (Ref: N14/08/102) as well

as on the National Health Research Database (Ref: WC_2014RP10_967). A waiver of informed consent was granted.

Results

A total of 370 patients were analysed (Figure 1).



[a]Human Immunodeficiency Virus; [b]Tuberculosis

Figure 1.Flow diagram depicting study population

The prevalence of HIV was 38.4% (n=142) (unknown status: n=78, 21.1 %), with only 48.6% (n=69) of HIV-positive patients receiving anti-retroviral therapy (defaulted n=8, 5.6%; unknown if on treatment n=31, 21.9%). The median absolute CD4 count was 230 cells/µL (25^{th} – 75^{th} percentile 61 to 420) in the 95 patients who had a documented absolute CD4 count.

The prevalence of tuberculosis was 13.5% (n=50), although the majority of patients (n=233, 63%) did not had any investigations to exclude or confirm a diagnosis of tuberculosis. Forty-

four patients (88%) with active tuberculosis received treatment; four (8%) patients did not receive treatment while in hospital (treatment status unknown n=2, 4%). The HIV/tuberculosis co-infection prevalence was 10.8% (n=40).

The median age of patients was 40 years (25^{th} – 75^{th} percentile 28 to 56) with HIV and tuberculosis more likely in younger patients (Table 1). The acuity of most patients were at least very urgent (n=245, 66.2%).

Table 1. Patient demographics and acuity according to HIV and tuberculosis status in patients managed in the resuscitation area of Khayelitsha Hospital

	Overall (N=370)	**HIV-positive (n=142)**	**HIV-negative (n=150)**	**p-value**	**Tuberculosis confirmed (n=50)**	**Tuberculosis not confirmed (n=87**	**p-value**
Age (years) (Median(Q1Q3[a]))	40 (28-56)	36 (29-45)	46 (28-64)	0.001	36 (30-45)	49 (34-68)	0.001
Male n (%)	149 (40.3)	42 (29.6)	75 (50.0)	<0.001	22 (44.0)	44 (50.6)	0.42
Time spent in area (minutes) (Median (Q1-Q3))	270 (135-480)	289 (145-500)	285 (135-480)	0.957	380 (240-730)	287 (182-483)	0.021
Patient acuity[b] n (%)							
- **Non-urgent (Green)**	64 (17.3)	19 (13.4)	22 (14.7)	0.734	3 (6.0)	10 (11.5)	0.535
- **Urgent (Yellow)**	61 (16.5)	24 (16.9)	25 (16.7)	0.987	8 (16.0)	14 (16.1)	0.966
- **Very urgent (Orange)**	113 (30.5)	48 (33.8)	42 (28.0)	0.3	17 (34.0)	33 (37.9)	0.61
- **Emergency (Red)**	132 (35.7)	51 (35.9)	61 (40.7)	0.445	22 (44.0)	30 (34.5)	0.292

[a]Q_1-Q_3= 25^{th} – 75^{th} percentile; [b]According to the South African Triage Scale

The most frequent admissions to the resuscitation area during the study period involved intentional overdoses (n=60, 16.2%), the respiratory system (n=59, 15.9%) and the neurology

system (n=50, 13.5%). Intentional overdose and gastro-intestinal related admissions occurred more in the HIV-positive group (Table 2).

Table 2. Top five admission categories of patients managed in the resuscitation area of Khayelitsha Hospital, overall and according to HIV-status.

Admission category	Overall n (%)	HIV-positive n (%)	HIV-negative n (%)	p-value
Intentional overdose	60 (16.2)	21 (14.8)	13 (8.7)	<0.01
Respiratory	59 (15.9)	31 (21.8)	22 (14.6)	0.12
Neurological	50 (13.5)	16 (11.3)	30 (20.0)	0.04
Gastro-Intestinal	45 (12.2)	28 (19.7)	13 (8.7)	0.01
Cardiovascular	42 (11.4)	12 (8.5)	21 (14.0)	0.14

A total of 211 (57%) patients received a mobile chest x-ray, 167 (45.1%) had an electrocardiogram (ECG) and 73 (19.7%) had an ultrasound examination (Table 3). HIV-positive patients were more likely to be investigated by an abdominal ultrasound (p<0.001). An HIV rapid test was performed on 57 (15.4%) patients and sputum investigations for tuberculosis done in 10 (2.7%) patients. The administration of intravenous antibiotics (n=141, 38.1%) occurred significantly more in the HIV-positive group (Table 3).

Table 3. Diagnostic tests and therapeutic interventions performed in patients managed in the resuscitation area of Khayelitsha Hospital.

	Overall n (%)	HIV Positive n (%)	HIV Negative n (%)	p-value
Diagnostic test				
Mobile chest x-ray	211 (57.0)	90 (42.7)	105 (49.8)	0.23
Electrocardiogram (ECG)	167 (45.1)	63 (9.6)	74 (44.3)	0.4
Abdominal ultrasound (point-of-care or formal)	73 (19.7)	42 (57.5)	20 (27.4)	<0.01
Blood culture	70 (18.9)	44 (62.9)	20 (28.6)	0.41
Therapeutic intervention				
Intravenous antibiotics	141 (38.1)	78 (55.3)	45 (31.9)	<0.01
Intravenous potassium replacement	16 (4.3)	8 (50.0)	7 (43.75)	0.72
Continuous positive airway pressure	16 (4.3)	2 (12.5)	9 (56.25)	0.04
Intubation and ventilation	12 (3.2)	2 (16.7)	8 (66.7)	0.07
Inotropes	8 (2.2)	3 (37.5)	2 (25.0)	0.75

Half of the patients (n=186, 50.3%) were subsequently managed by in-hospital specialist teams of which 84 (45.2%) were HIV-positive and 34 (18.3%) had active tuberculosis disease (Table 4).

Table 4. Disposition of patients from the resuscitation area of Khayelitsha Hospital.

	Overall n (%)	**Active tuberculosis n (%)**	**HIV positive n (%)**	**HIV negative n (%)**	**p-value (HIV status)**
Managed by emergency centre staff outside the resuscitation area	101 (27.3)	1 (2)	29 (20.4)	37 (23.9)	0.48
Referred to specialist services within Khayelitsha Hospital	186 (50.3)	35 (70)	84 (59.2)	74 (47.7)	0.05
Referred to tertiary facilities	63 (17.0)	11 (22)	23 (16.2)	30 (19.4)	0.48
Died in resuscitation area	20 (5.4)	3 (6)	6 (4.2)	14 (9.0)	0.11
	370 (100)	**50 (100)**	**142 (100)**	**155 (100)**	

The in-hospital mortality during the study period was 17.0% (n=63). Twenty patients (31.7%) died in the resuscitation area, 28 patients (44.5%) with in-hospital teams at Khayelitsha Hospital and 15 patients (23.8%) who were referred to a tertiary facility. Neither HIV-status (p=0.27), nor tuberculosis status (p=0.27) were associated with all-cause in-hospital mortality. Overall, 16 (25.4%) deaths related to the respiratory system (pneumonia), 10 (15.9%) to the neurological system (cerebrovascular accidents, seizures, meningitis and hepatic encephalopathy), and 8 (12.7%) to each of the cardiovascular and gastrointestinal systems (including congestive cardiac failure and acute gastro-enteritis, respectively).

Discussion

This study describes the burden of tuberculosis and HIV on the resuscitation area of a district level hospital. HIV-positive patients place a unique burden on the resuscitation area of Khayelitsha Hospital with regards to intentional overdose and ultrasound examinations. The in-hospital mortality rate was high, but not associated with either HIV or tuberculosis status.

Our study findings suggest that the HIV prevalence of patients attending the emergency centre is substantially higher than the provincial prevalence. This is in contrast to data from a district level emergency centre in KwaZulu-Natal, where the HIV prevalence of emergency admissions was similar to the provincial prevalence (emergency centre prevalence 44.4%; provincial

prevalence 49.7%).[18] The HIV prevalence in our study (38%) was three times higher than the national HIV prevalence in 2016, despite the Western Cape having an HIV prevalence rate well below the national figure.[4] However, Khayelitsha has the highest antenatal HIV prevalence in the Western Cape (34%).[19] This would support a higher HIV prevalence in Khayelitsha than the rest of the Western Cape, despite taking into account that the antenatal HIV prevalence will be higher than the community prevalence as it reflects young sexually active females.

Nevertheless, the prevalence most likely indicate that HIV infection does in fact result in a disproportionate increase in admissions compared to HIV negative status.

The in-hospital mortality of medical patients presenting to the resuscitation area was substantially higher than trauma-related deaths from the same clinical area (17% versus 3%).[14] This is expected as the mortality rate in medical patients are usually higher than in other clinical disciplines.[20] The in-hospital tuberculosis mortality rate (22%) was very similar to the national tuberculosis mortality rate of 21% in 2015,[8] but substantially higher than the 6% of the Western Cape.[7] Nonetheless, it was similar to the global tuberculosis in-hospital mortality amongst persons living with HIV of 27% in 2016.[21] Neither HIV nor tuberculosis status correlated significantly with mortality, but our results may be confounded by the large proportion of patients that had an unknown tuberculosis and/or HIV status. More robust data regarding mortality rates in district level hospitals in South Africa is needed.

Intentional overdose related presentations occurred frequently, especially in the HIV-positive group. This is in keeping with a recent study at Khayelitsha Hospital where a fifth of intentional overdose related presentations occurred in HIV-positive patients.[12] Other African studies have shown a definite correlation between HIV/AIDS and suicidal ideation or attempt.[22,23] Associated factors seems to relate to the stigma of HIV/AIDS (e.g. feeling ashamed of status) as well as clinical factors such as a perception of poor physical health, physical pain, and being newly diagnosed.[23] Investigating underlying reasons for selfharm attempts were beyond the scope of the study, but needs to get attention. Apart from the HIV burden, the people of Khayelitsha are faced with multiple psychosocial intricacies such as poverty, unemployment, incomplete schooling, and high rates of violence (interpersonal, domestic and sexual).[24] It is therefore, not surprising that many patients encounter frustration and depression in such circumstances, and may contribute to suicidal ideation and depression.

Point-of-care and formal ultrasound was used notably more in HIV-positive patients. The frequency of its use is considerably higher than data from a HIV-cohort presenting to an

emergency centre in KwaZulu/Natal.[18] Ultrasound has been used to diagnose extra-pulmonary tuberculosis in mainly HIV positive patients,[25–27] despite the lack of robust evidence for its use. Abdominal ultrasound had a pooled sensitivity of 63% and pooled specificity of 68% in diagnosing bacteriologically confirmed HIV associated tuberculosis; however the review reported very low quality evidence and only included one study evaluating point-of-care ultrasound.[28] Issues encountered with point-of-care ultrasound in the emergency centre environment are that not all emergency doctors are proficiently trained in performing these investigations, which are operator dependant and may yield variable results depending on the user.[29] Formal abdominal ultrasound is also subject to the availability of proficiently trained sonographers in an already burdened radiology department, where imaging often only happens the following day or when sonographers are available.

Limitations

Several factors may have influenced the results of this study. One of the major limitations in this study was the large number of patients with an unknown HIV and/or tuberculosis status; a reflection of the large proportion of untested individuals in a high prevalent area (both HIV and tuberculosis). It is thus possible that the prevalence of these diseases may therefore be underestimated, and not be a true reflection of the actual burden of disease. The statistical inference of the study's results may also be biased due to the large number of missing variables, and, thus, acknowledged as such. It should also be noted that the study was confined to the resuscitation area and not all areas of emergency centre, and it is unclear what effect this will have on the actual disease burden on the emergency centre as a complete entity. Care should also be taken not to generalise the results of this study to other health districts, provinces or countries due to the small sample size and the unique population profile of Khayelitsha. Further studies of similar district level institutions, measuring similar parameters, would be needed in order to draw more objective conclusions to the initial research questions. Lastly, the actual causes of death were not analysed, and it remains unclear whether HIV and/or tuberculosis were just contributing factors or the actual cause of death.

Conclusion

This study highlights the influence of HIV and tuberculosis on the provision of acute care at a district level hospital. Despite this burden, the in-hospital mortality was not associated with either HIV or tuberculosis status indicating that the biggest impact on patient outcome seems to relate to the acuity of the presentation. The high prevalence of intentional overdose

presentations may speak to a larger underlying set of social vicissitudes which need to be addressed.

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Part C: SUPPORTING DOCUMENTATION

1. Research Protocol

The burden of HIV and TB on the resuscitation unit of Khayelitsha Hospital

Principal Investigator: Dr L Swarts

Division of Emergency Medicine

University of Stellenbosch

Supervisor: Dr DJ van Hoving

Division of Emergency Medicine

University of Stellenbosch

Abstract

Background: HIV/AIDS and TB place a massive burden on South Africa's health services with many individuals accessing the health system through hospital emergency centres when there have been delays to adequate diagnosis and treatment of infective complications (especially TB) in primary care settings. Patients presenting to emergency centres are often severely ill and prompt management is needed to decrease morbidity and mortality.[1] However, the burden of HIV and TB in emergency centres in South Africa is not well described, particularly in the era of widespread antiretroviral therapy availability that would be expected to reduce hospital presentations.

Objective: To determine the contemporary burden of HIV and TB on the resuscitation unit in the Emergency Centre of Khayelitsha Hospital.

Methods: A retrospective chart review will be performed. Twelve randomly selected weeks from the Khayelitsha Hospital resuscitation database (a prospectively collected observational database capturing all patients managed within the resuscitation area since 1 November 2014) will be the sampled. Trauma cases will be excluded. Patients with missing information will only be excluded on the sections pertaining to that particular variable. We foresee a sample size of about 350 patients. Variables to be collected are patient demographics (age / gender); patient acuity (according to the South African Triage Scale); TB and HIV infection status; CD4 count; reason for admission to the resuscitation unit; diagnostic tests performed and their results; interventions received while in the resuscitation unit; time spent in the resuscitation unit; disposition from the resuscitation unit; and in- hospital outcome. Data will be categorized and analysed in four groups relating to the TB and HIV status. The outcomes are the prevalence of HIV and active TB in patients admitted to the resuscitation unit; the comparison between the above mentioned groups regarding in-hospital mortality.

Conclusion: The rationale for this project lies in the fact that the burden of HIV- and TB-related medical emergencies is mainly dictated by disease prevalence. Limited data on the contemporary prevalence of HIV and active TB in emergency centres is currently available. The knowledge gained from this project will have logistic, human resource and financial implications. Training and preventive measures may also be strengthened.

1. Introduction 1.1.Background

Tuberculosis (TB) and Human Immunodeficiency Virus (HIV) are deadly communicable diseases, particularly in socio-economically deprived regions of the world. Despite the advancement of knowledge with regard to pathogenesis and treatment of these diseases over recent years, TB and HIV still pose a great health care burden on a global scale.

An estimated 36.9 million people were living with HIV at the end of 2014, with around 2 million people becoming newly infected and approximately 1.2 million people having lost their lives from HIV related causes.[2] Sub Saharan Africa accounts for almost 70% of the global total of new HIV infections and is the most affected region with 25.8 million people living with HIV in 2014.[2] In South Africa in 2012, an estimated 6.4 million people (12.2%) were HIV-infected; 1.2 million more than
in 2008.[3]

TB (pulmonary and extra-pulmonary) adds a similar burden. An estimated 9 million people developed TB globally in 2013.[4] The African region of the World Health Organization (WHO) had the second highest number of incident cases (2.6 million; 29%), but the highest incidence rate (280 vs 126 globally) and mortality rate (42 vs 16 globally) per 100 000 population.[4] In 2013, South Africa had the 6th largest absolute number of incident TB cases per country (between 410 000 and 520 000), but the 3rd highest incidence rate (860 per 100 000 population) in the world.[4]

HIV/TB co-infection increases the burden even more. TB remains the leading cause of death among people living with HIV, accounting for around one in five AIDS-related deaths.[5] However, this is likely an underestimation as many TB cases (~40%) are undiagnosed.[6] More than one million people (13%) diagnosed worldwide with TB in 2013 were HIV co-infected.[4] With HIV treatment advancements and growing knowledge among healthcare workers and the general population, TB related deaths among people living with HIV have declined by 36% worldwide from 2004 to 2013.[7] Despite this decline, the HIV-associated TB endemic still has high morbidity and mortality rates, especially in South Africa. In the Western Cape, HIV and TB were the 3rd (6%) and 4th (5.7%) leading causes of death, respectively, at the end of 2013.[8]

HIV infection is also associated with many other complications apart from TB and can involve any organ system. Serious complications that could be life-threatening relates to the

respiratory system (bacterial pneumonia, *Pneumocystis jiroveci* pneumonia), the cardiac system (pericardial disease, cardiomyopathy) and the neurological system (cryptococcal meningitis, toxoplasmosis).[9] However, few data are available on the exact impact of HIV and TB on emergency centres, specifically resuscitation units, in South Africa.

1.2.Rationale

The burden of HIV- and TB-related medical emergencies is dictated by disease prevalence, the availability of treatment, and the expertise of the primary health system. The rationale for this research project is to quantify the burden of HIV-and TB-related emergencies by determining the prevalence in the resuscitation unit of Khayelitsha Hospital.

The prevalence of HIV-related cases in emergency centres in South Africa is largely unknown with only one single-centre study indicating a 50% HIV prevalence in medical patients.[10] Currently, there is no data on the burden of HIV on emergency centres in the Western Cape, although more than 50% of medical admissions to Khayelitsha Hospital are HIV-related (Meintjes, unpublished). A similar knowledge gap exists relating to TB in emergency centres. Almost 15% of presentations to the Paarl Hospital emergency centre were attributed to TB;[11] whereas 33% of unselected HIV-infected patients at G.F Jooste Hospital were diagnosed with TB on the first day of acute hospital admission.[12]

Antiretroviral and anti-tuberculous treatment is available free of charge at government primary care clinics in South Africa but various problems still exists with stigma, diagnosis and treatment access. Reasons for this range from ignorance at patient and healthcare levels to problems related to the availability and accuracy of diagnostic tests. Co-infection with HIV further increases the diagnostic challenge, especially that of TB.[13]

1.3.Significance

HIV/AIDS and TB place a massive burden on South Africa's health services with many individuals accessing the health system through hospital emergency centres when there have been delays to adequate diagnosis and treatment of infective complications (especially TB) in primary care settings.[14] Patients presenting to emergency centres are often severely ill and prompt management is needed to decrease morbidity and mortality.[1] However, the burden of HIV and TB in emergency centres remains largely unquantified. The knowledge gained from this project will have logistic, human resource and financial implications. Training and preventive measures will also be strengthened.

1.4.Research Question

What is the burden of HIV and TB on the resuscitation unit of Khayelitsha Hospital?

1.5.Aim and objectives

The aim of the study is to determine the contemporary burden of HIV and TB on the resuscitation unit in the Emergency Centre of Khayelitsha Hospital

The objectives are:

- To determine the prevalence of HIV and TB in patients presenting to the resuscitation unit of Khayelitsha Hospital
- To determine the in-hospital mortality of patients with HIV and TB presenting the resuscitation unit of Khayelitsha Hospital
- To compare the in-hospital mortality of patients with HIV and TB to those without HIV and TB

2. Methodology 2.1.Study Design

A retrospective analysis of a prospectively collected observational database combined with a retrospective chart review to include additional variables.

2.2.Study Setting

Khayelitsha Hospital is a 240 bed hospital in the constantly expanding township of Khayelitsha, Cape

Town. It serves a health district with a population of more than 390 000, which are predominantly black African (99%).[15] The community is also faced with high levels of unemployment (38%), with a high disease burden of TB, HIV, and interpersonal violence.[15]

Khayelitsha Hospital provides inpatient services to the community such as medical, surgical, paediatric and obstetric, with an emergency centre 30% larger than for a standard district hospital in South Africa.[15, 16] The resuscitation unit consists of four adult beds and one paediatric cot, each equipped with its own monitor (blood pressure, pulse oximetry, and capnography capabilities) and a stand-alone ventilator. A fully stocked emergency trolley for airway management with a defibrillator is also available. The main admission criteria to the

resuscitation unit is a high acuity score, according to the South African Triage Scale (SATS).[17] The SATS takes into account vital sign parameters such as heart rate, respiratory rate, blood pressure and temperature and group patients into colour code categories. The colour codes suggest the urgency of the presenting complaints and recommend a time frame in which the patients should be assessed by a medical practitioner.[17] Alternatively a patient can be managed in the resuscitation unit at the discretion of any senior practitioner on duty

2.3.Study Population

The electronic Khayelitsha Hospital resuscitation database is a prospectively collected observational database capturing all patients managed within the resuscitation area since 1 November 2014. Data are captured electronically via a tailored smartphone application, are immediately coded and directly stored onto a password protected server. A decoding sheet is separately stored. The guarantor of the database (Dr van Hoving) also ensures that the clinical notes of captured patients are available on the Khayelitsha Hospital ECM (Enterprise Content Management) system (current capture rate ± 95%).

The main study has been registered at the Stellenbosch University Health Research Ethics Committee (Ref: N14/08/102 with amendment 24 June 2015) as well as at the National Health Research Database (Ref: WC_2014RP10_967).

We will randomly select 12 weeks from the Khayelitsha Hospital resuscitation database. A computer- based random number generator will be used. All patients admitted during these weeks will be eligible for inclusion, but trauma-related cases will be excluded (HIV is not a cause of trauma but incidental). Patients with missing information will only be excluded from analysis for those variables where information is missing.

We foresee a sample size of about 350 patients. This correlates to an estimated true proportion of 35%, a 10% confidence interval width and a desired precision of 5%.

2.4.Data Collection and Management

Data will be collected by the investigators on site at Khayelitsha Hospital after a decoded cleaned extract of the resuscitation database has been obtained (cleaned: copied into an Excel spreadsheet with all trauma cases removed). The Excel spreadsheet will then be further populated through the electronic clinical record, the National Health Laboratory Service web view, and the Clinicom information system. The following variables will be collected:

- Patient demographics (Age / Gender)

- Patient acuity (according to the South African Triage Scale)
- TB status (active TB or not)
- HIV infection status
- CD4 lymphocyte count if HIV-infected
- Reason for admission to the resuscitation unit
- Diagnostic tests performed
- Interventions received while in the resuscitation unit
- Time spent in the resuscitation unit
- Disposition from the resuscitation unit
- In-hospital mortality

Data will be entered onto a password protected Microsoft Excel® spreadsheet. The data will be stored on a password-protected computer, with a back-up copy on an external hard drive stored in a lockable cupboard in the Division of Emergency Medicine office, Stellenbosch University. Access to the data will be limited to the research team.

Data will be categorized into four nominal input variables:

- Group A = No active TB & HIV negative
- Group B = No active TB & HIV positive
- Group C = Active TB & HIV negative
- Group D = Active TB & HIV positive

An HIV positive case is defined as a laboratory confirmed HIV result (either prior to admission or during the admission). Patients with unknown HIV status will be reported as such, but two sets of analyses will be done; one excluding them and one including them with HIV negatives. An active TB case is defined as a laboratory confirmed result from any sample during the current admission or six months prior to admission, or patients who have been empirically diagnosed with active TB and started on TB treatment. **2.5.Data Analysis**

Summary statistics will be used to describe all variables. Distributions of variables will be presented with histograms and or frequency tables. Medians or means will be used as the measures of central location for ordinal and continuous responses and standard deviations and

quartiles as indicators of spread. The prevalence of HIV, TB and TB/HIV co-infection will be calculated using the total number of patients in the sample as the denominator.

The relationships between the continuous variables will be analysed using appropriate analysis of variance (ANOVA) tests or the Kruskal-Wallis test if the data do not meet the requirements for a parametric test. The Chi-square test will be used when categorical variables are compared. A 5% level of confidence will be used to determine significance.

Analysis will be duplicated. The first analysis will be done with the HIV-unknown cases excluded and then repeated with HIV-unknown cases categorised as HIV negative.

Data analysis will be done by the principal investigator with support from the supervisor using SPSS (version 22.0).

2.6.Time Schedule

- March 2016: Ethics and institutional approval
- April 2016 - June 2016: Data collection
- July 2016 - August 2016: Data analysis
- September 2016 - January 2017: Writing up and submission

3. Ethical Considerations

Risks and benefits: As this study will not involve direct or indirect patient care, risk to patients is likely minimal. The electronic resuscitation database is already part of another study project and has passed through an ethics committee in the process. Potential risk due to loss of patient data is however possible. For this reason identifying information will be removed as soon as the data collection for that specific patient is completed. Having a better idea of the specific burden related to HIV and TB at a district-level hospital may lead to improved emergency centre practices and resource allocation.

Informed consent process: The database from which the initial data will be drawn is registered with the

Stellenbosch University Health Research Ethics Committee (Ref: N14/08/102) as well as on the National Health Research Database (Ref: WC_2014RP10_967). The information obtained from the database will be supplemented with review of the patient record. As this will be retrospective, taking individual consent will be impractical.

Privacy and confidentiality: As described earlier, the study will make use of a combination of safeguards to ensure anonymity of study subjects. This will include on-site

data management using a Western Cape Government account and computers, a password protected Excel document containing the data sample, and coding data immediately after data collection is completed and removing identifying information.

As this is a retrospective study with no personal patient information being accessed, utilised or divulged, a waiver of informed consent is requested.

4. Limitations

This is a retrospective study using an existing database and therefor has inherent risks of error. Selection bias is primarily a result of either inappropriate inclusion or exclusion of subjects into the database or due to missing data. Inclusion criteria for the Khayelitsha Resuscitation database is well defined and should not lead to a significant error.

Missing data allow for selection bias by allowing preference for study subjects with complete data. Patients with missing data will be reported and will not be excluded from analysis; only the incomplete data points will be excluded. Missing patients from the database is also limited since the database manager regularly does quality checks to ensure all patients are captured. The Clinicom Hospital Information System, the ECM system and the resuscitation unit nursing register is used for this.

Data entered into the database may also be imprecise or invalid, resulting in information bias. This is again limited by the quality control performed by the database manager.

5. Reporting and implementation of results

Publication as an original article or short report in a peer reviewed journal is anticipated. The study results will also be distributed to the management team of Khayelitsha Hospital Emergency Centre and hospital administration. We will also prepare a policy brief for the provincial Health Impact Assessment Unit.

6. Resources 6.1.Resources utilisation

Resources used will be mainly non-clinical. This will include use of an existing Western Cape Government account and computers. As most patient information will be electronically available, Khayelitsha Hospital clerks will not be utilised to access hard copy folders. The investigators will not conduct the study when on-duty.

6.2.Budget

The budget for this study is: R 3250

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2. Ethics approval

Approved with Stipulations

New Application

26-Nov-2015

Mentoor, Lynne L

Ethics Reference #: S15/10/243

Title: The burden of HIV and TB on the resuscitation unit of Khayelitsha Hospital.

Dear Dr Lynne Mentoor,

The **New Application** received on **27-Oct-2015**, was reviewed by members of **Health Research Ethics Committee 2** via Expedited review procedures on **11-Nov-2015**.

Please note the following information about your approved research protocol:

Protocol Approval Period: **24-Nov-2015 -24-Nov-2016**

The Stipulations of your ethics approval are as follows:

1. **A waiver of informed consent is approved on the condition that at the point of data entry all data will be completely anonymised andaggregated.**

2. **HREC would like to alert the supervisor, Dr DJ van Hoving, that if there are plans moving forward to continue to access this database fromN14/08/102 for research purposes, that the database should be registered as such through an application to the HREC for the establishment of a database for research purposes.**

Please remember to use your **protocol number** (**S15/10/243**) on any documents or correspondence with the HREC concerning your research protocol.

Please note that the HREC has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

After Ethical Review:

Please note a template of the progress report is obtainable on www.sun.ac.za/rds and should be submitted to the Committee before the year has expired. The Committee will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit.

Translation of the consent document to the language applicable to the study participants should be submitted.

Federal Wide Assurance Number: 00001372

Institutional Review Board (IRB) Number: IRB0005239

The Health Research Ethics Committee complies with the SA National Health Act No.61 2003 as it pertains to health research and the United States

Code of Federal Regulations Title 45 Part 46. This committee abides by the ethical norms and principles for research, established by the Declaration of

Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes 2004 (Department of Health).

Provincial and City of Cape Town Approval

Please note that for research at a primary or secondary healthcare facility permission must still be obtained from the relevant authorities (Western Cape Department of Health and/or City Health) to conduct the research as stated in the protocol. Contact persons are Ms Claudette Abrahams at Western

Cape Department of Health (healthres@pgwc.gov.za Tel: +27 21 483 9907) and Dr Helene Visser at City Health (Helene.Visser@capetown.gov.za Tel: +27 21 400 3981). Research that will be conducted at any tertiary academic institution requires approval from the relevant hospital manager. Ethics approval is required BEFORE approval can be obtained from these health authorities.

We wish you the best as you conduct your research.

For standard HREC forms and documents please visit: www.sun.ac.za/rds

If you have any questions or need further assistance, please contact the HREC office at 219389819.

Included Documents:

CV D van Hoving

Application form

Declaration L Swarts

CV L Swarts

Protocol

Declaration D van Hoving

Protocol Synopsis

Waiver of informed consent request

Checklist

Sincerely,

Ashleen Fortuin

HREC Coordinator

Health Research Ethics Committee 2

Investigator Responsibilities

Protection of Human Research Participants

Some of the responsibilities investigators have when conducting research involving human participants are listed below:

1.Conducting the Research. You are responsible for making sure that the research is conducted according to the HREC approved research protocol. You are also responsible for the actions of all your coinvestigators and research staff involved with this research.

2.Participant Enrolment. You may not recruit or enrol participants prior to the HREC approval date or after the expiration date of HREC approval. All recruitment materials for any form of media must be approved by the HREC prior to their use. If you need to recruit more participants than was noted in your HREC approval letter, you must submit an amendment requesting an increase in the number of participants.

3.Informed Consent. You are responsible for obtaining and documenting effective informed consent using **only** the HREC-approved consent documents, and for ensuring that no human participants are involved in research prior to obtaining their informed consent. Please give all participants copies of the signed informed consent documents. Keep the originals in your secured research files for at least fifteen (15) years.

4.Continuing Review. The HREC must review and approve all HREC-approved research protocols at intervals appropriate to the degree of risk but not less than once per year. There is **no grace period.** Prior to the date on which the HREC approval of the research expires, **it is your responsibility to submit the continuing review report in a timely fashion to ensure a lapse in HREC approval does not occur.** If HREC approval of your research lapses, you must stop new participant enrolment, and contact the HREC office immediately.

5.Amendments and Changes. If you wish to amend or change any aspect of your research (such as research design, interventions or procedures, number of participants, participant population, informed consent document, instruments, surveys or recruiting material), you must submit the amendment to the HREC for review using the current Amendment Form. You **may not initiate** any amendments or changes to your research without first obtaining written HREC review and approval. The **only exception** is when it is necessary to eliminate apparent immediate hazards to participants and the HREC should be immediately informed of this necessity.

6.Adverse or Unanticipated Events. Any serious adverse events, participant complaints, and all unanticipated problems that involve risks to participants or others, as well as any research-related injuries, occurring at this institution or at other performance sites must be reported to the HREC within **five (5) days** of discovery of the incident. You must also report any instances of serious or continuing problems, or non-compliance with the HRECs requirements for protecting human research participants. The only exception to this policy is that the death of a research participant must be reported in accordance with the Stellenbosch University Health Research Ethics Committee Standard Operating Procedures www.sun025.sun.ac.za/portal /page/portal/Health_Sciences/English/Centres%20and%20Institutions/Research_Development_Suppor_t/Ethics/Application_package All reportable events should be submitted to the HREC using the Serious Adverse Event Report Form.

7.Research Record Keeping. You must keep the following research-related records, at a minimum, in a secure location for a minimum of fifteen years: the HREC approved research protocol and all amendments; all informed consent documents; recruiting materials; continuing review reports; adverse or unanticipated events; and all correspondence from the HREC

8.Reports to the MCC and Sponsor. When you submit the required annual report to the MCC or you submit required reports to your sponsor, you must provide a copy of that report to the HREC. You may submit the report at the time of continuing HREC review.

9.Provision of Emergency Medical Care. When a physician provides emergency medical care to a participant without prior HREC review and approval, to the extent permitted by law, such activities will not be recognised as research nor will the data obtained by any such activities should it be used in support of research.

10.Final reports. When you have completed (no further participant enrolment, interactions, interventions or data analysis) or stopped work on your research, you must submit a Final Report to the HREC.

11.On-Site Evaluations, MCC Inspections, or Audits. If you are notified that your research will be reviewed or audited by the MCC, the sponsor, any other external agency or any internal group, you must inform the HREC immediately of the impending audit/evaluation.

3. Author Guidelines: African Journal of Emergency Medicine

The instructions to authors are available from http://cdn.elsevier.com/promis_misc/AfJEM-GFA.pdf